

## Medical Progress

# Recent Advances in Neuroblastoma

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■ *Neuroblastoma is one of the commoner tumors of infancy and childhood. There is great variation in the histological picture and even within one tumor. One unique feature is the apparently high rate of spontaneous regression, particularly during the first year of life. There is also a tendency for neuroblastoma to mature to the more benign ganglioneuroma and recent in vitro studies suggest that a serum factor may influence this process. Approximately 90 percent of patients with neuroblastoma excrete abnormally high quantities of various catecholamines, thus providing a useful diagnostic tool and a means for evaluating the effect of therapy.*

*Treatment requires a multidisciplinary team approach involving a surgeon, radiotherapist and chemotherapist. Prognosis is influenced by a number of host factors and the most important of these seem to be the patient's age at diagnosis and the extent of the disease, although some children with widespread disease appear to have a particularly good prognosis. It is difficult to evaluate the influence of chemotherapy on survival in patients with neuroblastoma but it has not been of great significance. The unique biologic characteristics of this tumor require further study in the hope of providing more effective therapy.*

NEUROBLASTOMA IS A MALIGNANT neoplasm arising from embryonic sympathetic neuroblasts and may originate from the adrenal gland or sympa-

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thetic ganglia. With few exceptions it is a tumor of childhood and accounts for 8 percent of deaths from cancer in children. In children it ranks third in frequency to leukemia and central nervous system tumors.<sup>1</sup> Nevertheless, it is a rare condition and the yearly incidence ranges between 5 and 10 new cases per million children under 15 years of age.<sup>2</sup> Of 1,191 cases in the United States and Canada between the years

1961 and 1965, 30 percent occurred in the first year of life and the incidence declined exponentially with advancing age. In 19 cases the diagnosis was made at birth and nine more on the second or third day of life.<sup>3</sup>

This review is intended to summarize some recent advances in the understanding of the pathophysiology of neuroblastoma and to discuss newer concepts of treatment.

### Pathophysiological Considerations

There is great variation in the histopathological picture from tumor to tumor and within the same tumor. At one end of the spectrum are undifferentiated cells which are very difficult to distinguish from those of small cell sarcoma and at the other end are tumors which consist solely of mature cell types. Between these two extremes the tumors may exhibit varying degree of differentiation.

#### *Neuroblastoma and Ganglioneuroblastoma*

Beckwith<sup>4</sup> has devised the following histopathologic grading of neuroblastomas which includes the so-called ganglioneuroblastomas.

- Grade I. Predominantly differentiated: over 50 percent differentiating elements.
- Grade II. Predominantly undifferentiated: 5 to 50 percent differentiating elements.
- Grade III. Slightly differentiated: under 5 percent differentiating elements.
- Grade IV. Undifferentiated: no recognizable neurogenesis.

Histologic grade could be related to prognosis. In one series Beckwith found that five patients with Grade I tumor all survived beyond two years whereas three of four with Grade II tumor, four of 13 with Grade III and only one of 28 with Grade IV disease survived. Similarly the Surgical Fellows of the American Academy of Pediatrics found that approximately 30 percent of patients with well differentiated or moderately differentiated tumor survived beyond two years without evidence of disease compared with only 9 percent of those with poorly differentiated neuroblastoma.<sup>5</sup>

#### *Ganglioneuroma and Maturation of Neuroblastoma*

Ganglioneuromas represent the benign end of the neuroblastoma spectrum. The tumors are

usually circumscribed and encapsulated. Their extensions often project from the main tumor and tenaciously entwine adjacent structures. They are often calcified on roentgenography and can produce elevation in urinary catecholamine excretion.<sup>6</sup>

For many years controversy has existed regarding reports of maturation of neuroblastoma toward the more benign ganglioneuroma.<sup>7-12</sup> The maturation to the more benign form appears to parallel the natural embryogenesis of the sympathetic nervous system.<sup>7</sup> Greenfield and Shelley reviewed 66 cases of neuroblastoma seen at the Johns Hopkins Hospital and found 11 cases with complete maturation to benign ganglioneuroma.<sup>12</sup> Virtually all reported transformed tumors have been found in a paravertebral position or some other extra adrenal location.<sup>11,12</sup> The rationale behind Bodian's use of vitamin B<sub>12</sub> as therapy for neuroblastoma was that since the vitamin is essential for the normal maturation of hematopoietic cells, it might enhance the maturation of neuroblastic cells to ganglioneuroma.<sup>13</sup> This approach has not been proved successful.

Further support for the concept of maturation has been the demonstration that immature neuroblastoma can differentiate into mature ganglion cells in tissue culture<sup>14</sup> and the recent identification of a factor which selectively stimulates the growth of sympathetic and embryonic spinal sensory ganglia.<sup>15</sup> This factor, a protein, was discovered by Levi-Montalcini and her coworkers and has been termed the nerve growth factor (NGF). It apparently exerts its effect by stimulating RNA synthesis and thus is specific in that tissues other than sympathetic and spinal sensory ganglia are not affected. Some of the biochemical characteristics of NGF have now been defined and because of its unique effect on cells of neural crest origin, intensive investigation has been undertaken of its role in the pathogenesis and maturation of neuroblastoma. Serum levels of NGF have been determined in a small number of patients with neuroblastoma, and elevated levels were found in some patients. Analysis of preliminary data is inconclusive with respect to the relationship between NGF and neuroblastoma regression. Further studies may provide additional insight into this and other factors which could influence the growth and maturation patterns of the tumor.

## *Neuroblastoma and Von Recklinghausen's Disease*

Chatten and Voorhees<sup>16</sup> in their study of familial neuroblastoma suggested the possibility that a developmental relationship exists between neuroblastoma and neurofibromatosis. This is supported by Bolande and Towler, who found ganglion cells or ganglioneuromatous tissue or both within the neurofibromas in six cases of Von Recklinghausen's disease.<sup>17</sup> They also found ultrastructural similarities between neurofibroma and neuroblastoma maturing into ganglioneurofibroma. They theorized that neurofibromatosis may in some instances be derived from disseminated neuroblastoma or apparently migrating neural crest cells, particularly in the syndromes of congenital neuroblastomas with multiple skin and visceral metastasis.

### *Immunologic Aspects And Neuroblastomas in Situ*

An important development in the study of neuroblastoma has been the demonstration of cell-bound immune reactions against host neuroblastoma cells when evaluated *in vitro*.<sup>18</sup> Using a colony inhibition assay in which they are able to demonstrate immune reactions against human transplantation antigens, the Hellströms found that lymphocytes from patients with neuroblastoma inhibited colony formation by neuroblastoma cells. Lymphocytes from mothers of patients with neonatal neuroblastoma were also inhibitory in this system. This work suggests that tumor-specific antigens are present on neuroblastoma cells and that immune mechanisms could play a role in determining the natural history of the disease.

These observations could also partly explain why infants with neuroblastoma have the highest rate of spontaneous regression associated with any human cancer.<sup>19</sup> It may also provide an explanation for the demonstration of small deposits of neuroblastoma tissue in approximately one in 200 autopsies performed on infants up to the age of three months.<sup>20-23</sup> This is 40 times the expected rate based on the incidence of the tumor in the childhood population as a whole.<sup>20</sup> Additional evidence related to an immune reaction was provided by Martin and Beckwith, who found that lymphocytic infiltration within the tumor is associated with an improved prognosis.<sup>24</sup>

One can therefore speculate that spontaneous

regression of overt tumor of neuroblastoma *in situ* is the result of a cell-mediated immune response. However, this does not provide an explanation of the high incidence of spontaneous regression and "cure" in infants, as compared with older children. One hypothesis relates to the reduced levels of humoral antibody in young infants and the possibility that the higher levels in older children could impair the accessibility of tumor cells to the lethal action of lymphocytes.

### *Biochemical Aspects*

Since the cells of the sympathetic nervous system and chromaffin tissue of the adrenal medulla are capable of synthesizing and secreting various catecholamines it is not surprising that tumors arising from these precursors secrete excessive amounts of these compounds. Increased formation of dopa, dopamine, l-norepinephrine and their metabolites is said to occur in the majority of patients with neuroblastoma. Chart 1 outlines the relevant metabolic pathways, and demonstrates the wide variety of compounds which might be excreted in excess. These metabolites are identifiable in urine and although there is great variability in the relative excretion of each compound, one can expect that approximately 90 percent of patients with neuroblastoma will have elevation in the urinary levels of vanilmandelic acid (VMA) or homovanillic acid (HVA) or both.<sup>26</sup> Thus determination of these two catecholic substances would allow for identification of the majority of neuroblastomas without resorting to more elaborate biochemical procedures. In doubtful cases it may be advantageous to measure the excretion of the other products of dopa metabolism. Measurement of VMA and HVA excretion is not only helpful in diagnosis but can and should be utilized as an index of therapeutic effect since levels of excretion tend to parallel clinical evolution of disease.<sup>26</sup> However, it must be emphasized that one cannot distinguish between ganglioneuroma and neuroblastoma on the basis of catecholamine excretion pattern alone. Neuroblastoma and pheochromocytoma are both neural crest tumors and may excrete similar products of metabolism. One biochemical distinction relates to the fact that pheochromocytomas excrete only VMA and its precursors.

The prenatal identification of congenital neuroblastoma has been reported by Voute.<sup>27</sup> Six mothers presented with symptoms in the eighth

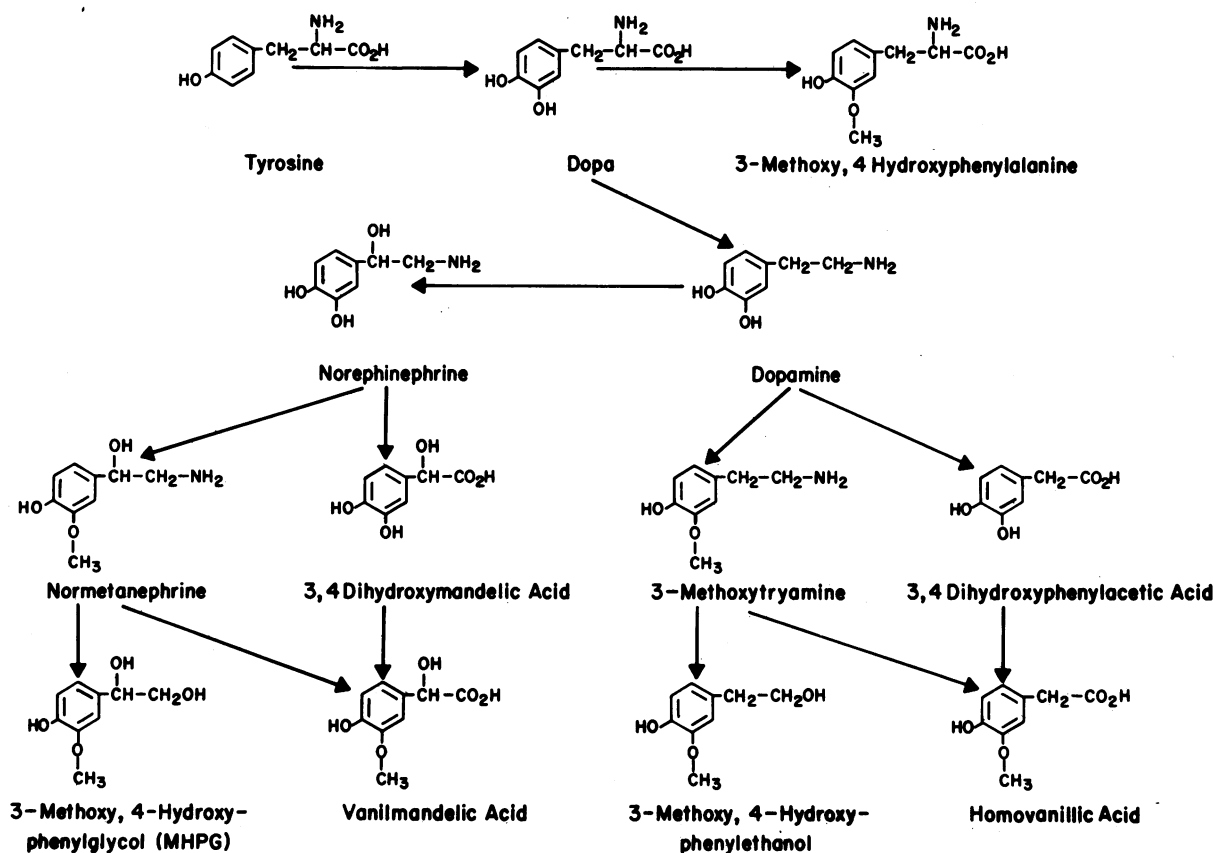


Chart 1.—Metabolic pathways in neuroblastoma (Williams and Greer<sup>25</sup>).

or ninth month of pregnancy similar to those of adults with a pheochromocytoma. These symptoms appeared to be caused by fetal catecholamines entering the maternal circulation and included attacks of sweating, paleness, tingling of hands and feet, headaches, decreased sensibility in fingers and toes, heart palpitations and in one case paroxysmal hypertension. Their offspring, three boys and three girls, were diagnosed as having neuroblastoma between day one and nine months of age, (two at birth, one at six weeks, one at ten weeks, one at two months and one at nine months). All infants had increased levels of urinary excretion of catecholamine metabolites. The symptoms exhibited by the mothers during pregnancy suggest that neurogenic tumors were functioning within the fetus. Analysis of the urine and blood from mothers such as these should provide further information and urinary metabolites and catecholamines should be assessed whenever pregnant women exhibit the appropriate symptoms during the last months of pregnancy.

A method for rapid determination for catecholamines has been developed and could be adapted as an office procedure.<sup>28</sup> As recommended by Gitlow et al the test is performed as follows:

1. To 4 drops (0.2 ml) of urine in a graduated centrifuge tube add 10 percent potassium carbonate to the 3 ml mark.
2. Add 4 drops of an equivolume mixture of 0.1 percent para-nitroaniline and 0.2 percent sodium nitrite and shake mixture.
3. Add isoamyl alcohol to the 4.5 ml mark.
4. Shake tube for 1 minute.
5. Compare visually against the standard similarly prepared from normal urine to which 5  $\mu$ gm of VMA had been added.

A negative urine gives rise to a colorless pale yellow or orange upper layer (isoamyl alcohol), whereas a positive test is one in which this layer has a pink or violet hue equal to or greater than the VMA standard. All the agents must be refrigerated until immediately before use. Para-nitroaniline is made by dissolving 1 gram of

para-nitroaniline in 20 ml of concentrated hydrochloric acid diluted to 1 liter with distilled water. Sodium nitrite should be prepared freshly each month. For the VMA standard 10 mg of VMA is diluted in 500 ml of water and 5 drops or 0.25 ml is added to 4 drops of urine. This test has been reported to have given negative results in 62 children with miscellaneous tumors and positive results in 32 of 35 patients with neuroblastomas.<sup>28</sup>

Cystathionine, an intermediate metabolite of methionine, is usually found in human brain, liver, kidney and muscle but is not normally present in urine. It has been detected in 50 percent of patients with neuroblastoma but its excretion appears to be independent of VMA, a fact which could make it a useful diagnostic test in the occasional patient in whom there is no elevation of urinary VMA or HVA. As with the catecholamines, its disappearance from the urine correlates well with clinical improvement.<sup>29</sup> D'Angio reported preliminary attempts to exploit the capacity of neuroblastoma to synthesize cystathionine from methionine through homocysteine by administering SE<sub>75</sub> labelled methionine to four children with metastatic neuroblastoma.<sup>30</sup> Localization of isotope using the scanning technique was seen within tumor three to six hours after the injection of the radionuclide in three of the patients. In two patients who underwent surgery, incorporation of the radioisotope was seen in excised tumor specimens. This procedure requires further investigation and may become an important diagnostic aid.

### Clinical Staging of Neuroblastoma

Prognosis in neuroblastoma is related to age of the patient, the presence or absence of bone marrow metastasis, and the degree of differentiation of the tumor cells. Evans et al<sup>31</sup> have proposed a staging scheme which describes the extent of the disease present without reference to resectability, because the latter includes the additional variables of surgical judgement and expertise. Where some authors tend to exclude children under one year of age from analysis because of the favorable prognosis in this age group and other authors include the degree of differentiation of the tumor, Evans acknowledges that the age of diagnosis does have prognostic significance but points out that it remains to be shown whether the extent of disease in infants influ-

ences their survival. She includes all neuroblastic tumors except pheochromocytoma and ganglioneuroma.

Stage O: Neuroblastoma *in situ*

Stage I: Tumor confined to the organ or structure of origin.

Stage II: Tumor extending in continuity beyond the organ or structure of origin but not crossing the midline. Regional lymph nodes on the homolateral side may be involved.

Stage III: Tumors extending in continuity beyond the midline. Regional lymph nodes may be involved bilaterally.

Stage IV: Remote disease involving skeleton, organs, soft tissues, or distant lymph node groups, etc.

Stage IV-S: Patients who would otherwise be Stage I or II but who have disease confined only to one or more of the following sites: liver, skin or bone marrow but without radiographic evidence of skeletal disease.

The proposed staging was applied to 100 children with neuroblastoma entered on two studies conducted by Childrens Cancer Study Group A. Short term survival data of this sample demonstrated the staging practical and it appeared to be of help in estimating prognosis. A special Stage IV category (IV-S) was developed because it was recognized that certain findings in children with neuroblastoma do not necessarily indicate as grave a prognosis as when similar circumstances occur in patients with other malignancies. Patients in the Stage IV-S category particularly those under 12 months of age have a good prognosis in spite of the widespread nature of the disease.<sup>32</sup>

### Treatment

Therapy directed against neuroblastoma must involve a multidisciplinary team approach. Surgeons, radiation therapists and chemotherapists all play a role in designing the treatment program even when one or other modality is not utilized in the initial plan of therapy.

Ideally, a tumor board consisting of representatives from the various disciplines should review each case from the point of view of adequacy of

diagnostic evaluation and in order to plan a rational and consistent treatment regimen. In this way, each patient derives the benefit of thorough review and ultimately enough data can be collected to allow for review of the success or otherwise of a particular program.

For convenience we will review the use of each of the current modes of therapy, bearing in mind that only close cooperation between the surgeon, radiation therapist and chemotherapist can result in optimal patient care. Since the approaches with x-ray therapy and surgical operation have been reasonably well standardized, they will be described first. The various drug regimens will be described and approaches being used by the various cancer chemotherapy groups will be outlined. Brief consideration will be given to an immunotherapeutic approach that might be used for treatment but must still be considered to be investigational.

### *Surgical Aspects of Therapy*

Completion of the clinical investigations usually requires one to two days. Roentgenographic studies and catecholamine determinations usually provide confirmation of clinical impressions so that the disease can often be diagnosed preoperatively. Anemia, if present, is corrected by the administration of red cells before operation. In view of the variability of presentation, the role and extent of surgical operation must be assessed in each case individually.

Tumors should be completely excised although most surgeons do not advocate en-bloc dissection of contiguous viscera.<sup>33</sup> Whether operation alone should be considered as definitive therapy in cases where the tumor is completely resected remains to be determined, particularly in children under one year of age. The role of postoperative chemotherapy in this patient group is currently under investigation. Surgically resected localized disease in the infant does not appear to warrant postoperative radiation therapy, although this is also in dispute.

The high probability of early metastasis should not discourage a surgical approach unless x-ray study, bone marrow aspiration or lymph node biopsy confirms the widespread nature of the disease. Histologic confirmation of the diagnosis should be made but a marrow aspirate infiltrated with tumor cells in a patient with increased urinary excretion of HVA or VMA is sufficient to

diagnose neuroblastoma. Often, the resectability of the tumor can be assessed only after laparotomy or exploratory thoracotomy, at which time a biopsy in non-resectable disease is indicated. However, most radiotherapists and chemotherapists are in favor of removing bulk tumor, leaving minimal residual disease to treat. Thus surgical resection of as much of the tumor as possible is an acceptable and probably desirable procedure in children with neuroblastoma, if it can be accomplished without undue hazard. There is insufficient data to answer the question as to whether the removal of the primary affects the growth of metastatic lesions.<sup>52</sup>

In addition to evaluation of the tumor from the viewpoint of resectability and the obtaining of adequate tissue for histological examination, the surgeon is in a position to provide information regarding extent of disease which may not be apparent from other diagnostic studies. Even in the presence of metastasis initial exploratory laparotomy, or thoracotomy, is often indicated with removal of bulk tumor and marking of residual disease with appropriate clips that can be followed postoperatively with roentgenologic studies. Control of disease as evidenced by improvement in clinical, radiologic, and biochemical parameters is often an indication for surgical re-exploration 12 to 18 months after the initial operation. At re-exploration the residual tumor, if any, is evaluated by biopsy and removed in toto, if possible.

Although there is little in the literature regarding complications secondary to anesthesia in patients with neuroblastoma, these patients can be a problem and blood pressure may have to be controlled with phentolamine. The preoperative use of an alpha adrenergic blocking agent such as phenoxybenzamine may be indicated.<sup>34</sup> Adrenocorticoid function may be depressed and additional hydrocortisone may be needed. Patients with secreting tumors may also need extra sedation in the preoperative period.

### *Radiation Therapy*

D'Angio has emphasized that all tissue at risk must be included in the treatment field, but no more than this and he advocates the use of external heavy metal blocks to shape fields appropriately.<sup>35</sup> Radiation dosage is usually adjusted according to age and mid plain doses delivered in the abdomen using 250 kv techniques range

from 1800 rads to an infant of less than 12 months to 3500 to 4000 rads to a child 4 to 5 years of age.<sup>35</sup> The dose is delivered over a period of two and a half weeks to four and a half weeks, depending on the child's age.<sup>36</sup> Children with neuroblastoma confined to the primary and adjacent lymph nodes should have all areas of tumor included in the treatment field. In planning localized radiation therapy, each extra adrenal site relates to different organs or tissues whose tolerance must be considered. Growing cartilage and growing bones demand attention in all sites. It is usually not possible to completely resect an adrenal neuroblastoma and the radiation therapy recommended uses curative doses with the daily dose of radiation conditioned by the size of the field and the nature of complications. Radiotherapy is well tolerated by children in the immediate postoperative period, but it seems reasonable to permit the patient to recover for one or two days before instituting therapy. Many radiotherapists now recommend inclusion of the entire width of the vertebral body in the irradiated field in order to minimize the incidence of scoliosis which results from asymmetrical irradiation of the vertebral growth centers.<sup>36,37</sup> However, even with this precaution, scoliosis can result from neurogenic involvement and fibrosis and contracture of soft tissues.<sup>36</sup> The liver can also be adversely affected by radiation as evidenced by reduced radioisotope uptake in areas included in the irradiation field. Tefft et al, in evaluating 115 children who received irradiation to the liver, found abnormalities in liver function with doses as low as 1200 rads.<sup>38</sup> The abnormalities appeared to be dose-related. Generally those patients who have abnormalities of liver function tests or liver scans in the acute phase will show some abnormalities in the chronic phase following irradiation. The incidence of severe clinical dysfunction in children is approximately 5 percent.<sup>38</sup> Care should be taken to exclude the kidneys from the direct radiation beam particularly if the contra-lateral kidney is outside the area of known tumor involvement. Should the kidneys both be involved one can consider attempting to shield one or both organs to limit the dose to within that tolerated by renal tissue. Another approach would involve attempting to eradicate the tumor using chemotherapy and thus eliminating the hazard of radiation nephritis.

Preoperative irradiation is not recommended since it tends to obscure the histological picture and we do not subscribe to the view that with such therapy more definitive surgical procedures can be undertaken. However, the approach can produce clinical regression of tumors and is advocated by Rissanen.<sup>39</sup> We consider that the patient with metastatic disease in whom surgical exploration is not contemplated is usually not a candidate for definitive radiation therapy until such time as chemotherapy or surgical operation or both have restricted the disease so that it is considered accessible to tumoricidal doses of radiation. In patients who have rapid development of spinal cord compression or in whom superior venacaval symptoms develop, high daily doses are warranted. A dose of 400 rads daily to a level of 1200 rads has been advocated by Young et al to assure rapid tumor shrinkage.<sup>40</sup> Increased edema concurrent with the radiation is not a major problem and the "field within a field technique" has been used to concentrate the dose to the critical area.

In cases of widespread dissemination, radiotherapy is administered with a palliative intent and is directed to either the primary site for control of symptoms as with bowel or bladder obstruction, intrathoracic problems or spinal cord compression. Palliative doses vary from 200 rads in one treatment to 600 rads in three consecutive days. However, as much as 2000 rads in 14 days may be required for relief of bone pain, treatment of localized or diffuse intracranial metastatic lesions, unsightly scalp masses, or control of intra-abdominal tumors.<sup>36</sup>

### *Chemotherapy*

The most widely used two agents in the treatment of neuroblastoma are cyclophosphamide and vincristine. These agents have been used alone in various dosage regimens or in combination as either sequential or alternating chemotherapy.<sup>41-47</sup>

Following James' report in 1965 of 100 percent complete or partial remission rate in children<sup>42</sup> of varying ages with unresectable neuroblastoma, it appeared that a highly effective combination of drugs was now available for treatment of this heretofore relatively unresponsive tumor. Unfortunately, using a similar regimen of alternating vincristine and cyclophosphamide in patients with metastatic disease, Evans et al, reporting for Chil-

drens Cancer Study Group A, found objective response in only nine of twenty-nine patients,<sup>46</sup> and of these only four were classified as attaining complete remission. Similarly disappointing results were reported by Sullivan et al in the Southwest Cancer Chemotherapy Study Group.<sup>45</sup> Certainly vincristine alone has been disappointing in this tumor system, as evidenced by remission rates of 22 percent in two independent studies.<sup>42,45</sup> On the other hand, cyclophosphamide has produced a much higher response rate even when used in conventional dosage schedules of 2.5 to 5 mg per kilogram of body weight per day.<sup>41</sup> Unfortunately these remission rates are deceptive since they relate to a temporary response; overall survival has not been significantly influenced by chemotherapy.

One approach is to administer larger amounts of an effective drug in order to obtain an improved therapeutic effect. The program is then limited only by an individual's tolerance to the drug. Whereas cyclophosphamide was usually administered in doses of 2.5 to 5 mg per kilogram of body weight per day, we have been impressed by rapid tumor shrinkage when doses of 10 mg per kilogram were administered daily either by mouth or intravenously.<sup>47</sup> Therapy is continued until the white blood cell count falls to between 1000 and 1500 per cu mm, which usually occurs in 10 to 14 days of treatment. Objective tumor regression was documented in nine of ten patients and complete remission occurred in eight. The treatment can be repeated every three to five weeks.

At present, drug treatment with cyclophosphamide alone or in combination with vincristine should be utilized in children with neuroblastoma. Whether or not infants with localized resectable disease should receive chemotherapy is a question currently being evaluated by Children's Cancer Study Group A.

In a situation such as this, where short-term responses to chemotherapy do not influence survival, a continuous search must be made for improved methods of treatment. A few new agents are under investigation; l-sarcosine and duanomycin have been given to a small number of patients with no dramatic results. Thus far, they have not been shown to be equal to either cyclophosphamide or vincristine as active agents for children with neuroblastoma.<sup>41-51</sup>

Bodian in the early 1960s suggested that patients with neuroblastoma respond to therapy with vitamin B<sub>12</sub>.<sup>13</sup> A survey published in 1965 by Sawitsky and Deposito revealed that American investigators were not able to show any increase in remission rate with either vitamin B<sub>12</sub> alone or in conjunction with radiation therapy or other chemotherapeutic agents in patients with advanced disease.<sup>52</sup> Recently the Medical Research Council in England sponsored an analysis of data from various investigators in the United Kingdom in order to evaluate the effect of vitamin B<sub>12</sub> in children with neuroblastoma.<sup>53</sup> This retrospective study failed to confirm that vitamin B<sub>12</sub> therapy is beneficial. Forty-three of 47 children whose treatment did not include vitamin B<sub>12</sub> were known to have died, compared with 56 of 61 children who received the vitamin in addition to other treatment. There appears to be no place for vitamin B<sub>12</sub> therapy in the modern approach to the treatment of neuroblastoma.

### *Immunotherapy*

Stimulated on the one hand by the poor results with conventional therapy in neuroblastoma and by the evidence for the existence of antigens peculiar to the neuroblastoma cell on the other hand, various investigators attempted to develop treatment programs based on immunotherapeutic principles. Lymphocytes from mothers or older siblings have been infused into patients on the premise that these lymphocytes may react against the tumor cells, as has been suggested might occur on the basis of *in vitro* studies in other centers. Preliminary studies at the New York Memorial Hospital<sup>54</sup> and other centers will, it is hoped, provide data to support or refute this concept.

### **Treatment Programs Based on Staging**

Stage I. Patients with localized disease should have the benefit of complete surgical resection, assuming that the primary site is technically accessible. Although many centers employ radiation or chemotherapy or both in this group of patients, control data is not available to either support or refute their use. If x-ray therapy is given it should be confined to the tumor bed, and postoperative chemotherapy should include cyclophosphamide in either conventional or high dose regimens for 12 to 18 months.

TABLE 1.—*Patients Surviving Two Years Free of Disease (From Breslow & McCann<sup>55</sup>)*

<i>Age at Diagnosis (months)</i>	<i>STAGES</i>					
	<i>I</i>	<i>II</i>	<i>III</i>	<i>IV</i>	<i>IV-S</i>	<i>All stages</i>
0-11 .....	11/12 (92%)	15/16 (94%)	2/4 (50%)	5/18 (28%)	18/19 (95%)	51/69 (74%)
12-23 .....	3/4 (75%)	3/17 (43%)	5/8 (62.5%)	0/25 (0%)	1/3 (33%)	12/47 (25%)
24+ .....	4/5 (80%)	4/12 (33%)	3/15 (20%)	3/93 (3%)	2/5 (40%)	16/130 (12%)
ALL AGES .....	18/21 (86%)	22/35 (63%)	10/27 (37%)	8/136 (6%)	21/27 (78%)	79/246 (32%)

Stage II and III. Patients with disease extending in continuity beyond the organ of origin are potentially curable. Surgical operation should be undertaken with a view to removing as much tumor as possible. It is extremely helpful in subsequent management if the surgeon has placed clips around the tumor bed or any area of residual area. Postoperative radiation therapy should be instituted but could be delayed in situations in which chemotherapy is to be used for tumor shrinkage when surgical removal was not accomplished. Chemotherapy utilizing cyclophosphamide with or without vincristine should be continued for at least 12 months.

Response to therapy is measured by clinical, radiological and biochemical factors. Those patients with primary tumors in the abdomen or pelvis who have responded to therapy and appear controlled are candidates for a "second-look" operation 12 to 18 months after the original surgical procedure.

Stage IV. Because of the widespread nature of disease in this group of patients, chemotherapy offers the only approach. Attempts at surgical resection or definitive radiation therapy cannot be expected to alter the poor outcome and these modes of therapy should be utilized for palliation only.

Stage IV-S. The accumulating evidence that these patients have an improved prognosis is apparently not related in any way to therapy. It appears logical to remove the primary tumor and administer chemotherapy postoperatively. Based on their review of 25 patients with Stage IV-S disease, D'Angio, Evans and Koop do not advocate radiation therapy and suggest that chemotherapy be considered only in patients with demonstrable bone marrow involvement.<sup>32</sup> Unfortunately it is unlikely that more definitive evaluation of the role of therapy will be forthcoming in this group of patients, since they are

few in number and most are under one year of age and thus have a higher likelihood of spontaneous regression.

### Prognosis

Survival is strongly influenced by the patient's age, extent of disease, degree of cell differentiation, the presence of skeletal and bone marrow metastasis. Breslow and McCann have analyzed data on 246 children, treated at the Childrens' Hospital of Philadelphia and in other institutions affiliated with Childrens Cancer Study Group A<sup>55</sup> (Table 1). Ninety-two percent of infants with Stage I disease survived, tumor-free, two years from diagnosis, compared with only 3 percent of those over 24 months of age with Stage IV disease. More than 50 percent of patients in this study had Stage IV disease and, irrespective of age, only 6 percent survived two years without disease. Thus for the majority of newly diagnosed patients the outlook is extremely poor. An improved prognosis has also been observed in patients with mediastinal primaries, but once again the major influence may be age, since most of the survivors tend to be in the younger age groups. Also there is a tendency for mediastinal tumors to be less undifferentiated and, as was mentioned previously, a number of investigators have been able to relate prognosis to the degree of histopathological differentiation.

To evaluate the impact of various modes of therapy on prognosis, a subcommittee of the Solid Tumor Task Force of the National Cancer Institute undertook a comparison of survival following treatment in children with neuroblastoma in each of two years, 1956 and 1962.<sup>56</sup> By 1962 the clinical use of vincristine and cyclophosphamide in patients with solid tumors was common. The data on patients from three chemotherapy study groups were considered together and there were no statistically significant differences in sur-

vival of children with neuroblastoma first seen in 1956 as compared with those diagnosed in 1962. The survival pattern of children with or without metastasis had not changed. Since radiation and surgical aspects of neuroblastoma management were considered to have been similar during the two study periods, it was concluded that the addition of new anti-neoplastic agents and the increased use of chemotherapy in 1962 had not improved the survival of children with neuroblastoma. Further investigation of the biological features of this unique tumor as well as the continued evaluation of new and improved methods of treatment must be pursued in order to improve the outlook for patients with this potentially curable neoplasm.

#### TRADE AND GENERIC NAMES OF DRUGS

*Oncovin*® ..... vincristine sulfate  
*Cytoxan*® ..... cyclophosphamide

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